THE REMARKS

Claims 12-15 and 17-21 are pending. Claims 12-15, 18 and 19 are rejected. The Office Action does not state whether Claims 17, 20, and 21 are allowed or rejection.

The Amendments

Claim 14 was previously amended in the Response to Office Action dated December 18, 2003; however, Applicants did not correctly identify the claim as "currently amended." Therefore, Applicants are re-submitting the same amendment in Claim 14 with the correctly identifier.

Claims 20 and 21 are amended to correct minor typographical errors in the space and hyphen.

No new matter is added in the amendments. The Examiner is respectfully requested to enter the amendment.

35 U.S.C. §103 Rejection

Claims 12-15, 18 and 19 are rejected under 35 U.S.C. §103 as being unpatentable over Gorodeski, *et al.*, *American J. of Physiol.*, Vol. 270, C1715-25. The rejection is traversed

Gorodeski, *et al.* disclose that ATP can acutely and reversibly modulate the paracellular permeability in cultures of human cervical cells. Gorodeski, *et al.* suggest a role for ATP in the cervix in vivo, in modulating the movement of fluid and solutes from the blood into the lumen, and in the secretion of cervical mucus, by increasing the tightness of the tight junctions (page C1715, right column, first full paragraph).

1. Gorodeski, *et al.* do not teach or suggest purinergic receptors, dinucleoside polyphosphates, or treatment of vaginal dryness.

Gorodeski, *et al.* disclose two types of **nucleotide receptors** (type I and Type II); Gorodeski, *et al.* do not teach or suggest **purinergic receptors**. Gorodeski, *et al.* only suggest a role for ATP in the cervix; Gorodeski, *et al.* do not teach or suggest that agonists of purinergic receptors affect the amount of or properties of the cervical and vaginal mucosa. Further,

Gorodeski, *et al.* do not teach or suggest the use of dinucleoside polyphosphates (Claims 12-15, and 20). There is no hint in Gorodeski, *et al.* regarding treating vaginal dryness (Claim 17-19 and 21).

2. Applicants are the first to discover the invention and have shown the invention works in vivo.

Applicants are the first to discover that dinucleoside polyphosphates of Formula II are potent agonists for purinergic receptors found in cervical and vaginal epithelia preparations. The methods of the present invention stimulates a patient's own production and secretion of mucins as well as increasing the levels of mucosal hydration, which serve to maintain the natural protective and lubricant characteristics of vaginal and cervical mucosa (see page 4, line24, through page 5, line 1). Applicants have provided prophetic examples in the application. Example 2 describes an in vivo study in rabbits, which evaluates the cervical mucins of a vaginal smear. Example 3 describes an in vivo study in ovariectomized monkeys, which evaluates the vaginal atrophy index.

Applicants are submitting herewith a copy of *Fertility and Sterility*, 79: 393-398 (2003), entitled "Selective $P2Y_2$ Receptor Agonists Stimulate Vaginal Moisture in Ovariectomized Rabbits." This article is co-authorized by Dr. Yerxa and Mr. Shaver, who are co-inventors of the present application. The article shows that $P2Y_2$ receptor agonists, dinucleotide polyphosphate INS 365 (P^1, P^4-di(uridine 5'-)tetraphosphate) and INS 45973 (P^1-(inosine 5'-), P^4- (uridine 5'-) tetraphosphate), increased vaginal moisture in ovariectomized rabbits. The article also shows that $P2Y_2$ receptor mRNA was localized to endocervical and cervical gland, epithelium, and stratified squamous epithelium of the vagina.

3. Gorodeski, *et al.* do not render the present claims obvious.

Gorodeski, *et al.* only disclose that ATP can affect the transudation or secretion of fluid from blood into the cericovaginal canal. Gorodeski, *et al.* do not identify ATP as a purinergic receptor agonist or suggest that purinergic receptors agonists can function the same as ATP.

The mechanism that Gorodeski, *et al.* teach is different from that of the present invention. Dinucleoside polyphosphates act in the present invention not by causing an increase in

transudation of fluid from the blood or plasma across membranes. Rather, dinucleoside polyphosphates act by causing a secretion of mucins from vesicles within the membrane itself. Stimulation of tissues with dinucleotides causes a dose dependent release of mucins from goblet cells in cervical tissue and a release of chloride and thus water from cervical tissue.

Absent hindsight construction using Applicants' invention as blueprint, a skilled person would not take the teaching of Gorodeski, *et al.* to (a) duplicate the base and add phosphate, and (b) expect it to work and treat an individual in need of treatment.

Luthje, *et al.* (Eur. J. Biochem. 173: 241 (1988)) describe "In contrast to ATP and ADP, which are rapidly degraded by ectonucleotidase present on blood cells and on the endothelial lining, the dinucleotides are only slowly degraded." (Page 245, left column, lines 10-12 from the bottom) This reference only shows that dinucleotides have longer half-life in blood than ATP or ADP. Dinucleoside polyphosphates may be in general more stable than mononucleotides, either chemically or biologically. However, dinucleotide polyphosphates do not work in every instance where mononucleotide works, and a skilled person would not simply replace ATP with dinucleotides absent hindsight construction.

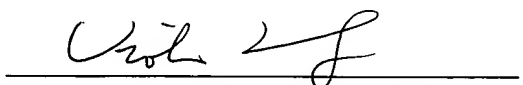
Therefore, Claims 12-15, 18 and 19 are not obvious over Gorodeski, *et al.*

CONCLUSION

In view of the foregoing amendments and remarks, the Applicants believe the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8181.

Respectfully submitted,

Date: February 3, 2005



Viola T. Kung (Reg. No. 41,131)

Enclosure: *Fertility and Sterility*, 79: 393-398 (2003)

HOWREY SIMON ARNOLD & WHITE, LLP
2941 Fairview Park Drive, Box 7
Falls Church, VA 22042
Tel.: (650) 463-8181